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Obesity: Should treatments target visceral afferents?

Terry L. Powley *, Michael M. Chi, Lindsey A. Schier, Robert J. Phillips

Purdue University, Department of Psychological Sciences, 703 Third St., West Lafayette, IN 47907, United States

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Abstract

The fact that obesity is a chronic disorder has traditionally focused experimental attention on the long-term controls of energy balance. Searches for therapeutic targets tend to concentrate on central integrative mechanisms and to largely ignore the visceral afferents and other peripheral mechanisms providing short-term controls of energy balance. Investigations of central mechanisms have yet to yield, however, any practical and effective treatments for correcting obesity. In this review, we survey some of the arguments for considering peripheral visceral afferent mechanisms as promising targets for future research on obesity. These arguments include (1) the observation that visceral afferents have the specializations, complexities, heterogeneities, and extensive distributions at key sites to provide exhaustive and dynamic feedback to control energy handling, (2) the fact that the most effective treatments yet developed for achieving long-term or permanent weight loss, namely gastroplasty and similar bariatric surgical procedures, clearly alter visceral afferent feedback from the gastrointestinal tract, and (3) experimental observations that suggest loss of visceral negative feedback can lead to overeating, positive energy balance, and obesity. Furthermore, even though excess adiposity is a disturbance in long-term energy regulation, it is instructive that obesity in the final analysis is developed, is maintained, and ultimately needs to be treated one meal at a time. When these considerations are taken in conjunction with concerns about side effects and risks that can be expected to accompany pharmacological therapies directed at central nervous system circuits, it would seem prudent to assess ways in which the feedback of visceral afferents might be enhanced or manipulated to support or synergize with other therapeutic strategies used in the management of excess energy intake.

Keywords: Vagus; Mechanoreceptors; Chemoreceptors; Bariatric surgery; Energy balance

1. Introduction

The visceral afferents innervating the gastrointestinal (GI) tract provide CNS control mechanisms with information about the ingestion, digestion, absorption, and metabolism of energy. In fact, given the relatively rapid rates at which individuals normally ingest nutrients [48] and the relatively slow rates at which postabsorptive and humoral signals are mobilized, visceral afferents supply most of the feedback available during and immediately after the cessation of a meal. Thus, visceral afferents play prominent roles in the processes collectively considered "satiation."

Food intake is controlled by a multiplicity of both short-term and long-term mechanisms. Short-term controls determine the length or size of bouts of feeding or the extent of a meal; these mechanisms include most prominently the neural signals and early endocrine adjustments produced by the contact with and consumption of food. Long-term controls of feeding determine how often and when bouts of ingestion occur; such long-term mechanisms include the humoral and later endocrine feedback associated with the distribution, metabolism, and storage of energy. Thus, short-term mechanisms monitor and adjust the early preabsorptive events involved in ingestion, whereas long-term mechanisms regulate the postabsorptive handling of energy [27,45].

Obesity is a long-term disturbance of energy regulation, often an intractably chronic one. This truism is commonly translated into the assumption that treatments for obesity should perforce target the long-term controls over ingestion. The assumption appears to be reasonable enough, and it has stimulated much work and generated many exciting new observations on the long-term feedback signals (e.g., leptin, insulin, etc.) and the central nervous system circuits that translate these signals into efferent outflows. But, for all the

* Corresponding author. Tel.: +1 765 494 6269; fax: +1 765 496 1264.
E-mail address: powleytl@psych.purdue.edu (T.L. Powley).

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reasonableness of the premise that treatments for obesity will be found in such long-term control mechanisms and for all of the intriguing discoveries about the CNS circuitry (e.g., arcuate nucleus and paraventricular nucleus) involved in such mechanisms, attempts to translate the information about central circuitry into a treatment for obesity have been singularly unsuccessful. For evidence of this lack of success, one only has to note the alarming increases in the incidence of obesity that have occurred (cf. Flegal and Popkin, this issue) even as extensive and programmatic research efforts have searched for effective treatments based on long-term signals [15,49].

Almost all models of the neural control of ingestion and energy balance also recognize a role for visceral afferents by incorporating the pathways into their circuitry. Most of these explanations of energy balance, however, treat visceral signaling as basic background information—as primitives or givens—that higher stations of the neuroaxis then use in generating integrative responses. Perhaps because of this prevailing view of afferent signals, relatively little attention has been given to the two alternative possibilities that visceral afferents could play more extensive and more flexible roles in determining ingestion and that such afferents might be targets for therapies designed to treat obesity.

In the present review, we survey observations that contradict the prevailing assumptions about visceral afferents. We also re-examine the presumption that a successful treatment for obesity should be focused simply on manipulating one or more of the signals or central circuits involved in long-term regulation of energy balance. We explore several arguments that challenge the adequacy of this assumption. We also consider the idea that designing treatments for obesity that directly target and try to optimize short-term feedback mechanisms limiting ingestion at the same time that these therapies concomitantly manage long-term controls might be more effective. *Our argument is not to ignore long-term controls, but rather not to ignore short-term controls either*.

As indicated above, visceral afferents supply much of the short-term or direct feedback that controls feeding. The afferents in the vagus nerve in particular carry most of the low-threshold non-nocioceptive information about the mechanical and chemical properties of food to the brain by way of the nucleus of the solitary tract that receives both gustatory and general visceral information. In a series of observations of the vagal afferent fibers in the GI tract, we have repeatedly been impressed with the variety, the complexity and specializations, and the dense and regionalized distributions of these endings [2,4,5,17,31,33,34,36,38,39,47]. The complexity and extent of the different types of afferent endings raise the question of whether or not these afferents function only to provide the modest and unspecialized signals, the primitives, presumed in most neural models of feeding. Similarly, the complexity and specializations that have been discovered in the afferent limb of the visceral nervous system also raise issues as to whether or not these endings are appropriate targets for treatments of obesity or other ingestive disorders.

Insufficient information is yet available to adequately answer these questions about vagal afferent innervation. In keeping with the theme of this symposium, however, we would like to explore some of these tentative ideas and discuss how they might be addressed experimentally. For purposes of this reconsideration we draw on several types of observations. First, we survey recent observations on visceral afferents that have begun to delineate how extensive and varied meal-related feedback may be. These observations are covered in the Methods and Results sections immediately below. Next, in the General discussion section, we explore some potential implications of visceral afferent organization and function for treatments of obesity. In particular, we examine briefly several ideas that suggest that basing treatment strategies exclusively on manipulation of long-term regulatory loops is unlikely to be successful. Some of these ideas emerged in the course of the discussions at the IBRC symposium encapsulated in this issue of *Physiology and Behavior*. Finally, we consider some of the particular ways in which visceral afferents might be important targets in a broad-based treatment for obesity that simultaneously and directly manages both long- and short-term control mechanisms.

2. Methods

2.1. Characterizing and mapping visceral (vagal) afferents

Although vagal afferents—or visceral afferents more generally—have traditionally been considered simple "free nerve endings" in the wall of the gut, limited both in number and complexity, neural tracer techniques have recently made practical direct examinations of these fibers. Observations with such tracers contradict the assumptions about visceral afferents that have been incorporated into most neural models of ingestion and energy balance.

To obtain more detailed observations about afferents, a series of similar protocols have been used. We have reviewed the protocols in full elsewhere [37] as well as, of course, in the relevant experimental reports. In brief, however, the strategy is to employ different tracers (in different experiments and separate animals) that are selectively incorporated by afferent neurons. Such tracers are injected into the vicinity of the afferent cell bodies. The somata of the vagal visceral afferents to the abdominal organs of ingestion are all located in the nodose ganglion immediately outside the skull. Since the nodose is heavily encapsulated, it is practical to inject the appropriate tracer into the ganglion without significant leakage. Once incorporated into a cell, the tracer gives that neuron a unique chemical label or phenotype that can then be recognized and localized with the appropriate histochemical processing.

For the examples of injections summarized here, we have used micropipettes (tip inner diameters = ~15 to 25 μm) to pressure inject small volumes (1 to 4 μl) of the tracer into the ganglion, typically into both the left and right nodose. After the injections, the animals (Sprague Dawley rats in this case) are maintained for a period of time to allow tracer to be incorporated into the cells and then transported actively to the peripheral terminals of the afferents. By timing the post-injection survival period appropriately (it varies according to